THE ACTION OF PRESSOR AMINES PRODUCED BY PUTREFACTION

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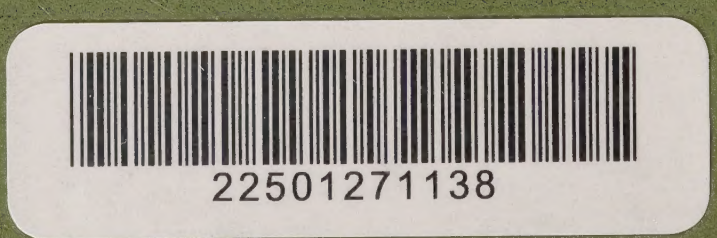
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THE ACTION OF PRESSOR AMINES PRODUCED BY PUTREFACTION.

By H. H. DALE and W. E. DIXON.

(*From the Pharmacological Laboratory, Cambridge, and the Wellcome Physiological Research Laboratories, Herne Hill*[1].)

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I. Introductory.

The physiological activity of the amines which are formed when carbon dioxide is split off from amino-acids, by putrefaction or otherwise, has recently been recognised and has acquired interest in several distinct connexions. Abelous[2] and his co-workers first observed the rise of blood-pressure caused by intravenous injection into animals of extracts from putrid meat. The substances causing this effect have been identified by Barger and Walpole[3] as isoamylamine, phenyl-ethyl-

[1] The experiments at Cambridge were performed by W. E. Dixon: those at Herne Hill by H. H. Dale.

[2] *C. R. Soc. de Biol.* I. pp. 463, 530. 1906.

[3] This *Journal*, XXXVIII. p. 343. 1909.

amine, and *p.* hydroxyphenylethylamine. They demonstrated the origin of the last from tyrosine, and there can be little doubt that the first and second are similarly formed from leucine and phenyl-alanine respectively. In the light of their results Rosenheim[1] examined substances which he had previously prepared from certain placental extracts, which one of us (W. E. D.) with F. E. Taylor[2] had found to produce rise of blood-pressure and contraction of the pregnant uterus. He was thus able to show that one of his substances was certainly and the others probably identical with those isolated by Barger and Walpole, and that their presence was probably the result, in this case also, of incipient putrefaction. More recently G. Barger, working with one of us (H. H. D.)[3], has found that *p.* hydroxyphenylethylamine and isoamylamine are present in watery extracts of ergot, the former being responsible for almost the whole of the pressor action of the liquid extract. In the present paper we describe in detail the action of isoamylamine and *p.* hydroxyphenylethylamine, these being the most abundant of the active amines obtained from the above mentioned natural sources, and each being, moreover, a representative member of a series of related and similarly active compounds. As the actions of the two bases are in most respects similar, it will be convenient to consider them together in the case of each of the organs and tissues examined.

II. Action on the circulatory system.

As stated above the action on the blood-pressure was the first indication observed of the specific activity of these bases. We have observed the action on the circulation in cats, dogs and rabbits; the animals were in all cases anæsthetised with ether, A.C.E. mixture or urethane, or had the brain completely destroyed by pithing. No significant difference in action exists between different animals, and the action in the cat, which has been most frequently the subject of experiment, may be taken as typical for all. An experiment on man is mentioned in a later section.

Of the two amines *p.* hydroxyphenylethylamine is considerably the more active. 1 mgm. of this base, or of its hydrochloride, dissolved in water and injected intravenously causes a sudden and pronounced rise of arterial pressure reminiscent of that produced by adrenaline. The

[1] This *Journal*, xxxviii. p. 337. 1909.

[2] *Lancet*, ii. p. 1158. 1907.

[3] This *Journal*. *Proc. Phys. Soc.* May 15th, 1909.

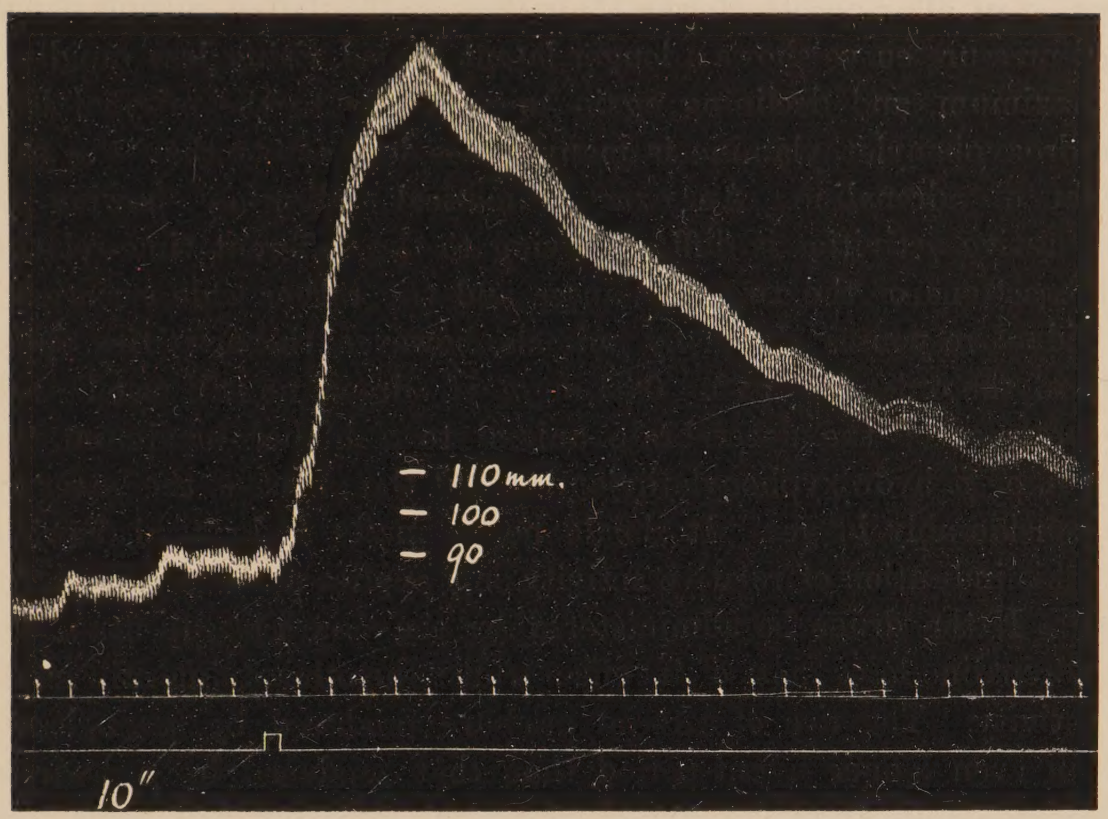


Fig. 1. Reduce to ¾. Blood-pressure of a pithed cat. Effect of 1 c.c. $\frac{N}{10}$ isoamylamine hydrochloride, injected into the femoral vein.

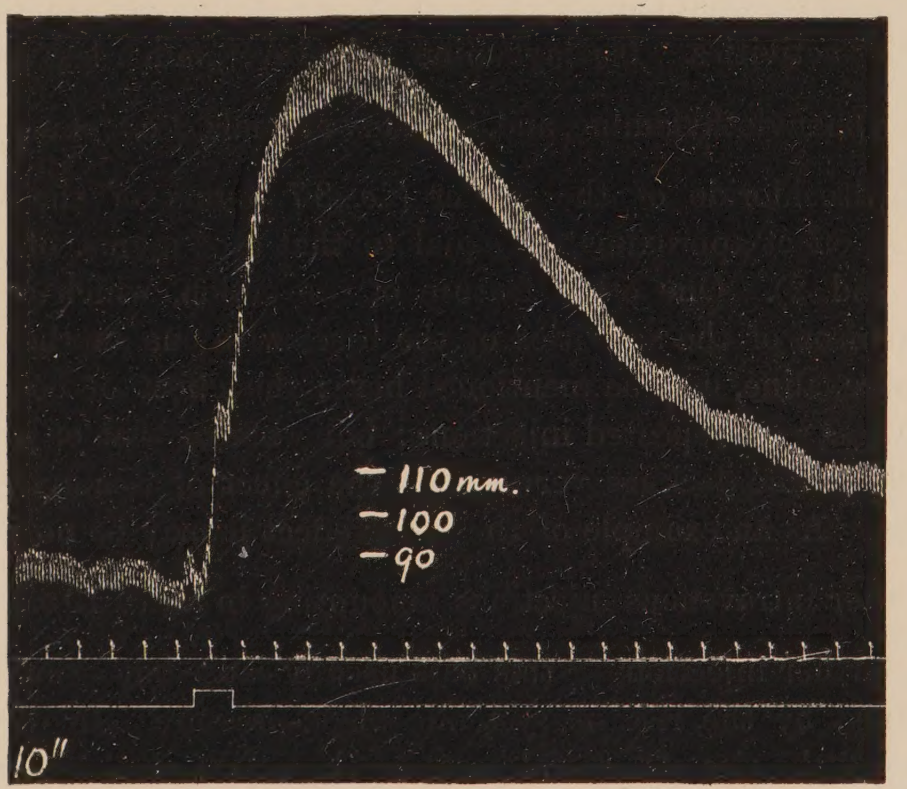


Fig. 2. Same experiment as Fig. 1. Red. ¾. Effect of 2 mgms. of *p.* hydroxyphenylethylamine.

effect is in all respects slower than that of the latter substance; the blood-pressure curve shows a longer latent period, rising less rapidly to its maximum, and declining again more slowly to the original level. *p.* hydroxyphenylethylamine is many times less active than the same weight of adrenaline. An exact numerical indication showing the comparative activities is difficult, owing to the different time-relations of the actions of the two substances and the rather wide variation of individual response. In many animals, however, the activities appear to be of the order of 1 : 20. 0·05 mgm. of adrenaline will usually raise the pressure of the decerebrate animal to a higher maximum than 1 mgm. of *p.* hydroxyphenylethylamine, but the effect of the latter will last considerably longer. It should be distinctly understood, however, that this indication of relative activity only applies under the conditions given. If the drugs be administered by the mouth or subcutaneously the adrenaline loses most of its effect whilst the other amine still retains its activity. The rise of arterial pressure produced by isoamylamine has an even longer latent-period than that produced by *p.* hydroxyphenylethylamine and the first effect is often a distinct fall in pressure. The pressor action is more slowly developed and more persistent than that of *p.* hydroxyphenylethylamine, when the doses of the drugs are such as to give rise to the same maximum. Here again, individual differences of reaction make it difficult to give a numerical indication of the relative activities. Isoamylamine is, however, much less active than *p.* hydroxyphenylethylamine, and, in many animals, 1 c.c. of a $\frac{N}{10}$ solution of the hydrochloride of the former (*i.e.* 8·7 mgms. of the base) will produce an effect approximately equal to that of 2 mgms. of the latter (Figs. 1 and 2). One other feature of the action, which complicates the comparison of the activities of the bases with one another and with that of adrenaline, may be mentioned here: the effect of both becomes gradually less with repeated injections; but whereas that of *p.* hydroxyphenylethylamine declines very slowly, the effect of isoamylamine falls off rapidly. As an example of the latter effect it may be noted that, in the cat, after intravenous injections amounting in all to 10 c.c. of the $\frac{N}{10}$ solution, further injections of this base usually cause but a small response as measured by the rise of systemic blood-pressure. In determining the cause of the rise of arterial pressure the action on the heart and on the arterioles must be considered separately.

A. *The heart.* Cardiometer records show that in the case of

both bases the rise of arterial blood-pressure must be partly due to increase in the output of the heart. Fig. 3 shows the effect in the case of *p.* hydroxyphenylethylamine. The effect on the heart's activity is also well shown by adding either base to the Ringer-Locke solution whilst perfusing through the coronary circulation of an isolated heart. It will be seen from Fig. 4 that *p.* hydroxyphenylethylamine causes an almost immediate increase in the frequency and amplitude of the

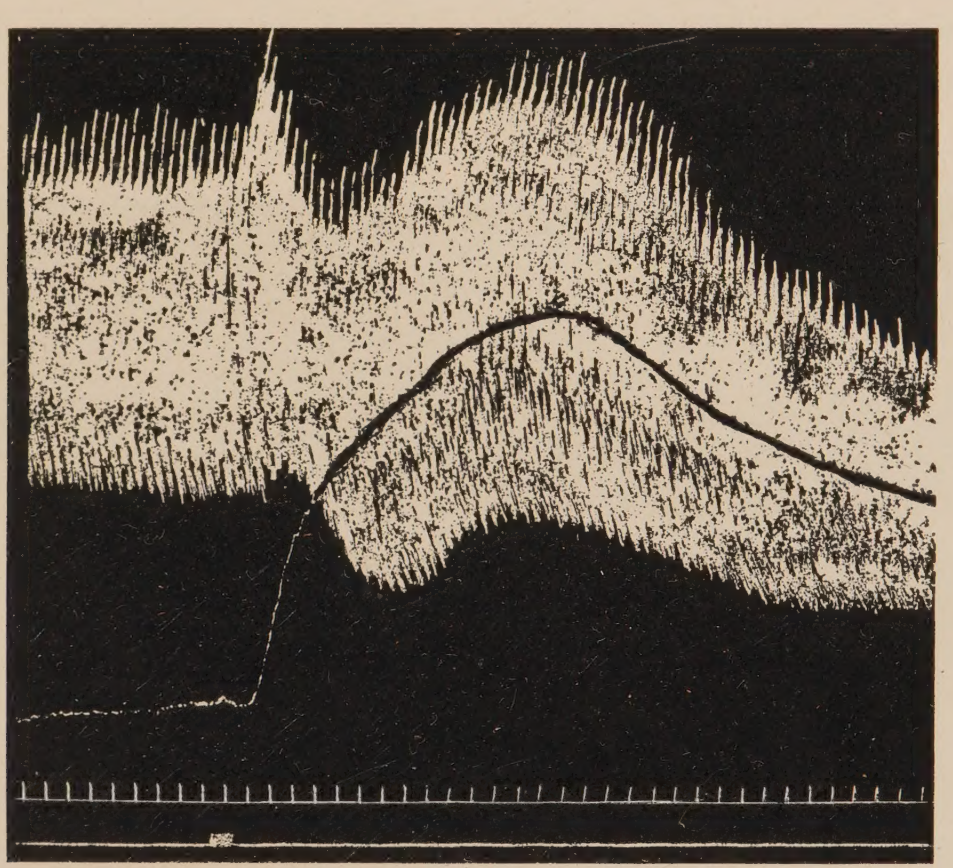


Fig. 3. Red. ¾. Cat. Urethane. Cardiometer and blood-pressure. Effect of 1 mgm. of *p.* hydroxyphenylethylamine. Downstroke represents systole. Time = 8 seconds.

ventricular beat, which persists for some time after the drug has left the circulation: it produces no initial inhibition. Isoamylamine, on the other hand (Fig. 5), produces at first a very marked decrease in the rate and vigour of the beat, which, if a sufficiently large dose has been given, may lead to temporary cessation. This initial inhibitor phase, which is represented on the blood-pressure curve by the primary fall, is succeeded by an increase in rapidity and amplitude of the heart-beat comparable to that produced by *p.* hydroxyphenylethylamine, but with the usual difference as regards dosage. The initial weakening of the beat by isoamylamine appears to be due to a direct depressant action on the heart-muscle. It is not due to action on the local vagus-

mechanism, since the effect is uninfluenced by the previous administration of atropine. It is accompanied by a marked retardation of outflow from the coronary vessels, which is too great to be accounted for by any decreased activity of the muscular walls of the heart. The coronary retardation slowly passes off and gives place to some acceleration of outflow. Both bases, when injected into the normal circulation of an animal, act like other pressor substances on the medullary centres; they cause reflex inhibition of the heart through the vagi. Section of these nerves, or their functional exclusion by atropine, is therefore necessary for the full development of the pressor effect.

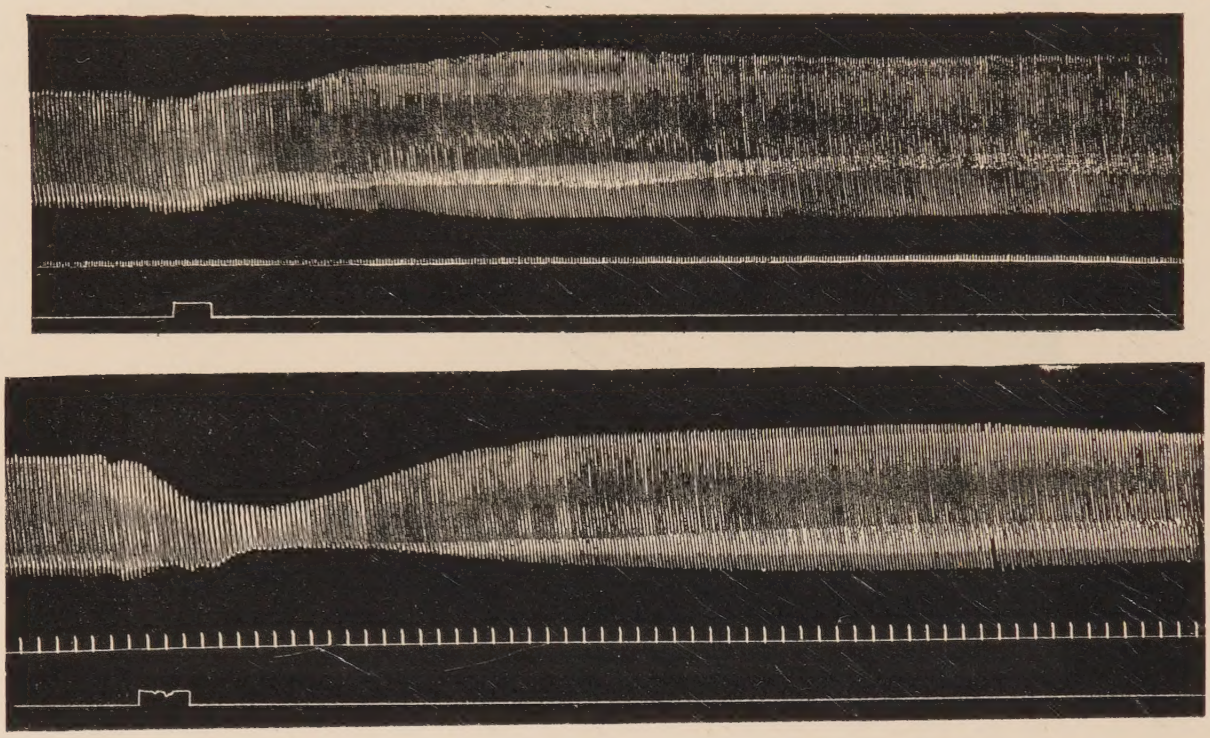


Fig. 4. Red. $\frac{2}{3}$. Isolated rabbit's heart. Effect of 0·2 mgm. of *p*. hydroxyphenylethylamine. Time = $\frac{1}{4}$ second.

Fig. 5. Red. $\frac{2}{3}$. Same experiment as Fig. 4. Effect of 0·2 c.c. $\frac{N}{10}$ isoamylamine hydrochloride. Time = 2 seconds.

B. *The arterioles.* The participation of arterial constriction in the pressor effect of these bases can be shown by the plethysmograph, or by perfusion of isolated organs whilst recording the outflow. Fig. 6 shows a plethysmographic record from a dog's ear. Similar results were obtained with a loop of cat's intestine and with a hind limb. The vessels perfused were those of the hind limbs of a cat, of the small intestine of the dog, and of the cat's lung. The method used was

that described by Brodie and Dixon[1]. The perfusing fluid was oxygenated Ringer under constant pressure. Both bases caused marked diminution in the rate of outflow from the veins of the limbs and of the intestines. These experiments show that the vaso-constrictor effect is, at any rate to a large extent, peripheral in origin (Figs. 7 and 8). In the case of the lung the first qualitative difference in the action of the two bases was observed. *p.* hydroxyphenylethylamine resembled adrenaline in producing no constriction of the pulmonary arterioles, differing from the latter substance only in producing a less decided dilator effect on those vessels. Isoamylamine, on the other hand, produced a decided diminution

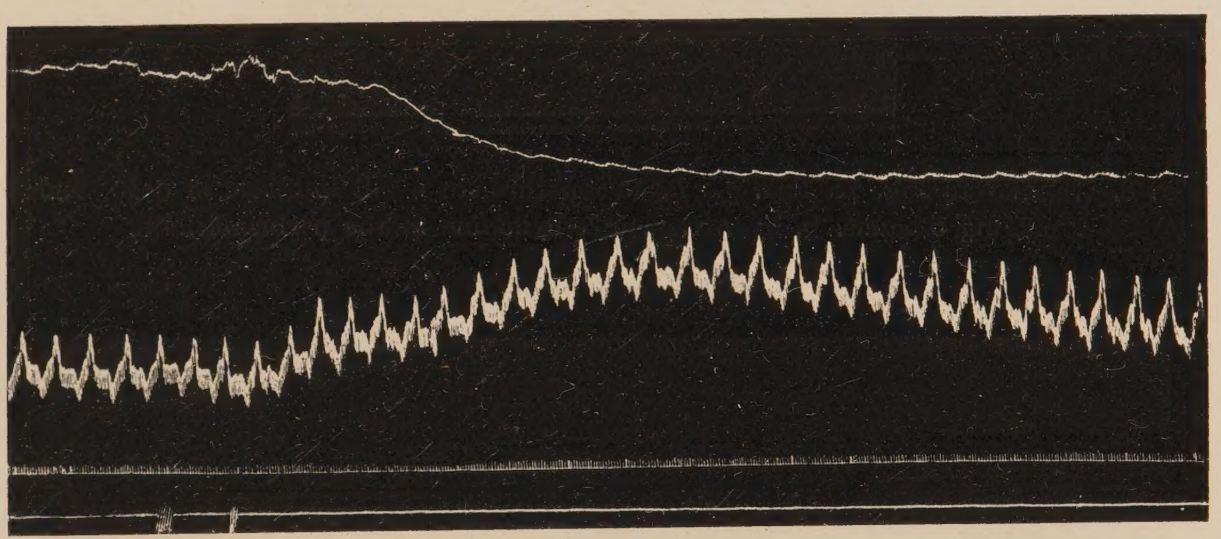


Fig. 6. Red. $\frac{2}{3}$. Dog. Morphine and urethane. Record of ear-volume and blood-pressure. Zero of blood-pressure 35 mm. below signal-line. Effect of 1 mgm. *p.* hydroxyphenylethylamine. Time = seconds.

Fig. 7. Red. $\frac{2}{3}$. Record of rate of perfusion through hind-limbs of a cat. Effect of adding 0·5 c.c. $\frac{N}{10}$ isoamylamine hydrochloride to the perfusion-fluid. Vertical lines represent the effect of adding 5 c.c. saline solution to the receiving flask. Time = seconds.

[1] This *Journal*, xxx. p. 476. 1904.

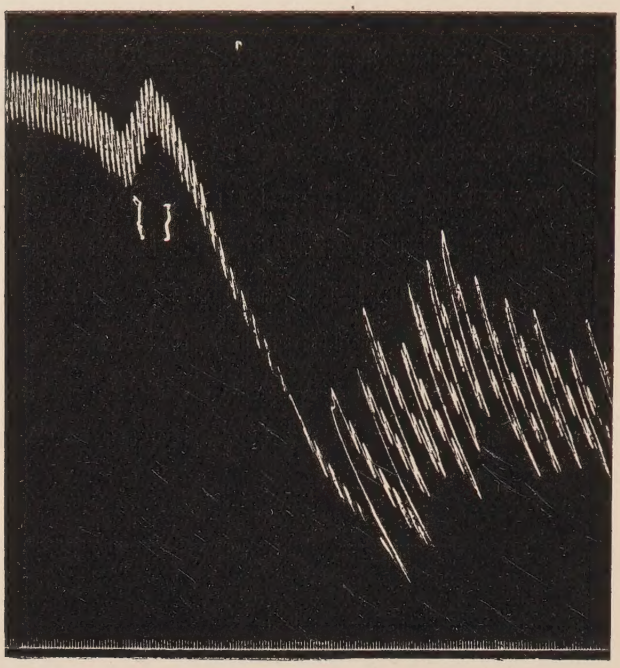


Fig. 8. Similar to Fig. 7. Red. $\frac{3}{4}$. Perfusion through small intestine of dog. Effect of adding 5 mgms. *p.* hydroxyphenylethylamine to the perfusion-fluid.

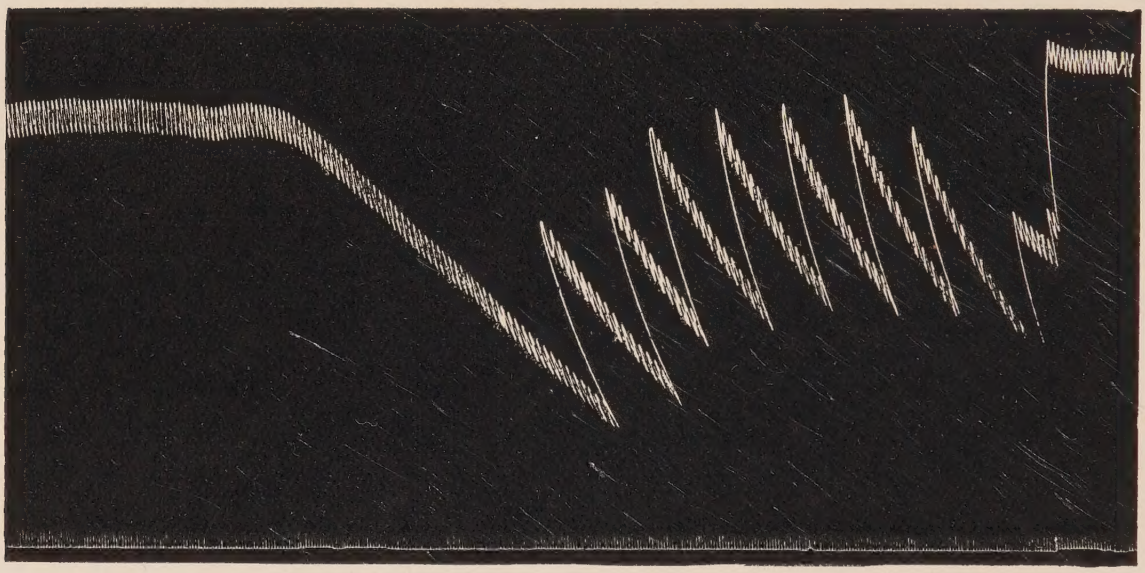


Fig. 9. Similar to Figs. 7 and 8. Red. $\frac{2}{3}$. Perfusion through lung of cat. Effect of adding 2 c.c. of $\frac{N}{10}$ isoamylamine hydrochloride to the perfusion-fluid.

of the outflow from the pulmonary veins, which could only be interpreted as indicating constriction of the arterioles. With smaller doses (1 c.c. $\frac{N}{10}$ solution) this was followed by a secondary dilation: with larger doses (2 c.c. $\frac{N}{10}$ solution) the constriction was more persistent (Fig. 9).

III. The spleen.

The muscular capsule of the spleen closely follows the arterial musculature in its reaction to drugs. It was, therefore, expected that both these bases would cause contraction of the spleen, and this was found to be the case (cf. Fig. 10). The time-relations of the effect were similar to those of the rise of blood-pressure.

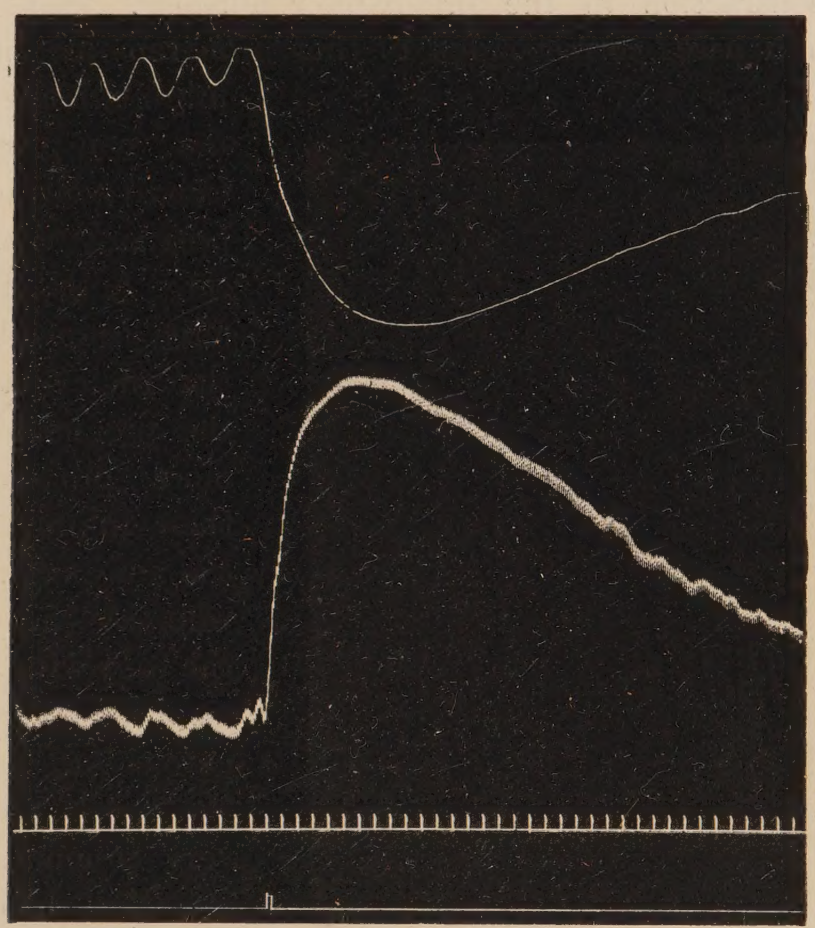


Fig. 10. Red. $\frac{3}{5}$. Pithed cat. Spleen-volume and blood-pressure. Effect of 2 mgms. of *p.* hydroxyphenylethylamine intravenously. Time = 10 seconds.

IV. The bronchioles.

The action on the plain muscle of the bronchioles was also examined by the plethysmographic method. It was found that *p.* hydroxyphenylethylamine had no effect whilst isoamylamine induced a very slight constriction.

V. The uterus.

In some animals, such as the rabbit, the uterine muscle resembles that of the arteries in its response to sympathetic nerve impulses and

to adrenaline[1]. Both *p.* hydroxyphenylethylamine and isoamylamine were found to cause contraction of the uterus and vagina of the rabbit in all functional conditions.

The reaction of the cat's uterus was of special interest on account of the change in response to sympathetic nerve-impulses and to adrenaline which this organ undergoes with change in its functional state, the response being inhibition of tone and rhythm in the non-pregnant condition, contraction in the pregnant condition[2]. Here again the action of both bases corresponded to that of adrenaline in that both inhibited the activity of the non-pregnant and caused contraction of the pregnant uterus of the cat. Both of them differed from adrenaline in that their motor effect on the pregnant was much more pronounced than their inhibitor effect on the non-pregnant uterus, whereas the reverse is the case with adrenaline. In a non-pregnant multiparous cat, injections of the two bases which had very pronounced effects on the blood-pressure caused but trifling inhibition of the uterine contractions. At a later stage of the same experiment, when, subsequent to large injections of nicotine, the uterus had acquired a considerable degree of tone, more marked inhibitory effects were observed with both bases: at no stage, however, in this or other

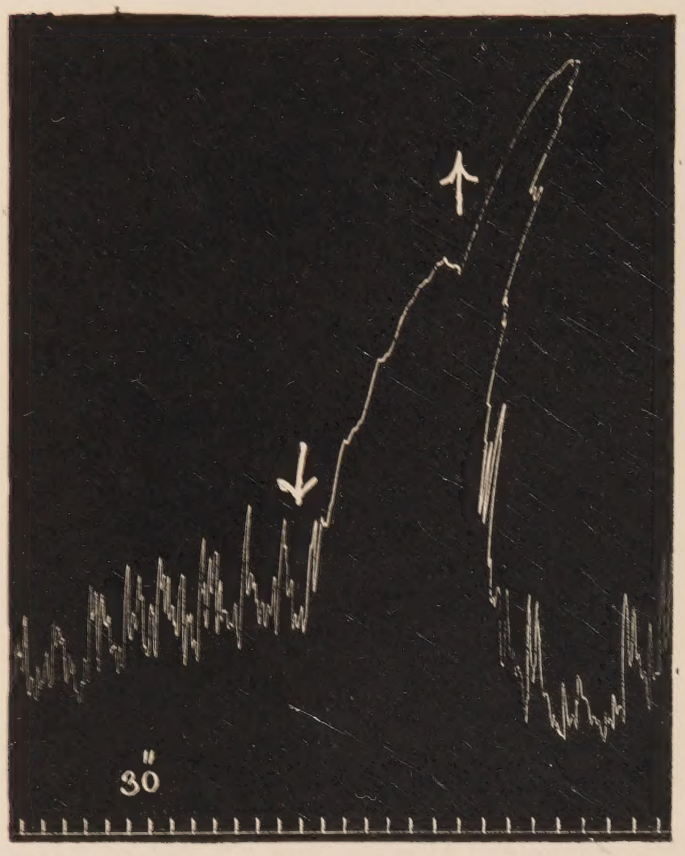


Fig. 11. Red. $\frac{2}{3}$. Isolated horn of virgin cat's uterus. Effect of 1 c.c. $\frac{N}{10}$ isoamylamine hydrochloride. At ↓ the drug was added, at ↑ a change was made to pure Ringer's solution. Time = 30 seconds. Downstroke = Contraction.

[1] Langley and Anderson. This *Journal*, XIX. p. 122. 1895. Langley. This *Journal*, XXVII. p. 252. 1901.

[2] Dale. This *Journal*, XXXIV. p. 189. 1906. Cushny. This *Journal*, XXXV. p. 1. 1906. Kehrer. *Archiv f. Gynäkol.* LXXXI. p. 160. 1906.

experiments, was the inhibition induced by injection of these drugs nearly so pronounced as that caused by an injection of adrenaline, though the latter was only present in such an amount as to produce a smaller effect on the blood-pressure than those given by the bases. The virgin cat's uterus gave a more pronounced inhibitory response. Figs. 11 and 12 show records of the isolated horn of such a uterus, suspended in oxygenated Ringer's solution at 37° C. (Kehrer's method). The effect of the drug was obtained by adding 1 c.c. of $\frac{N}{10}$ isoamylamine hydrochloride and 2 mgms. of *p.* hydroxyphenylethylamine hydrochloride respectively to the 250 c.c. of Ringer's solution in the

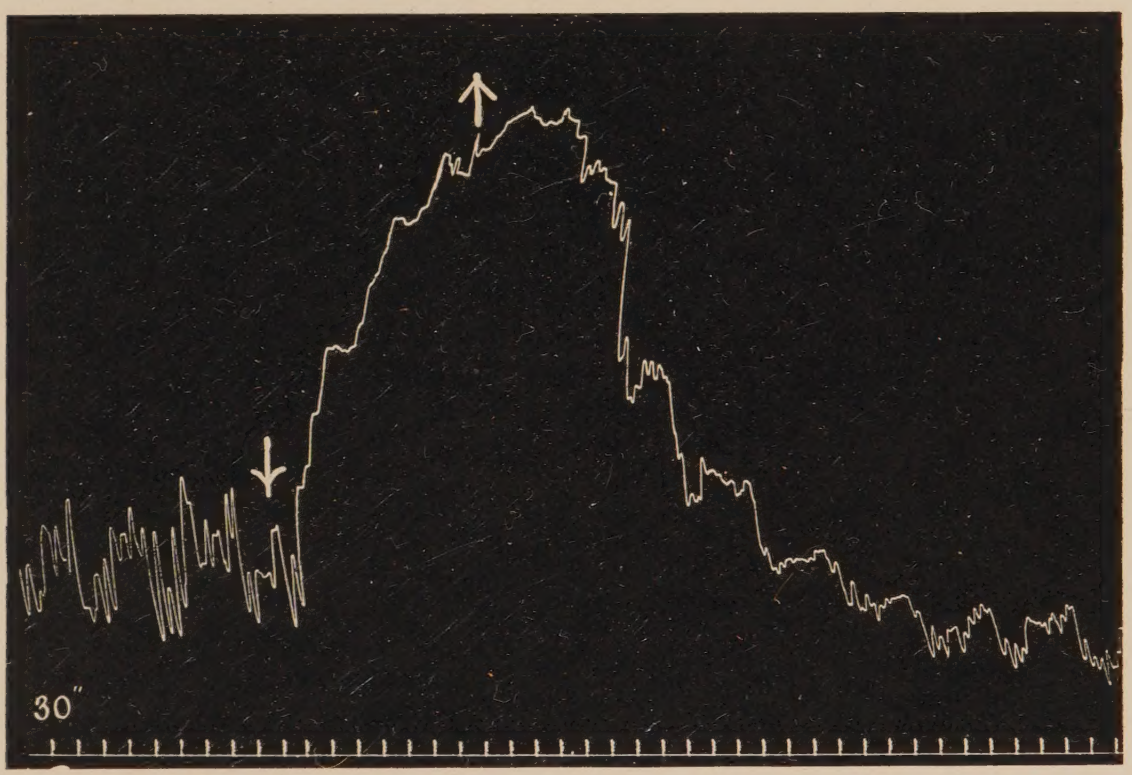


Fig. 12. Red. $\frac{2}{3}$. Same as Fig. 11. Effect of 2 mgms. of *p.* hydroxyphenylethylamine.

bath. By the same method was obtained the tracing, from the horn of a cat's uterus at about the middle of pregnancy, reproduced in Fig. 13. The effect of 1 c.c. of $\frac{N}{10}$ isoamylamine was practically identical. The long latent-period of the contraction, which both bases evoke in the previously quiescent organ, is probably due to the time necessary for diffusion through the greatly thickened peritoneal investment of the pregnant uterus. Change to pure Ringer's solution causes disappearance of the large rhythmic contractions which the

bases had set up and return to the original condition of moderate tonus and freedom from rhythm.

Though the pregnant uterus is thus stimulated to contraction we have not found it possible to bring on labour in pregnant animals by injection of either base. A cat near the end of pregnancy was given 5 mgm. of *p.* hydroxyphenylethylamine intramuscularly and 5 mgms. intravenously. Acceleration and strengthening of the heart-beat was observed and a strong contraction of the uterus was felt through the abdominal wall,

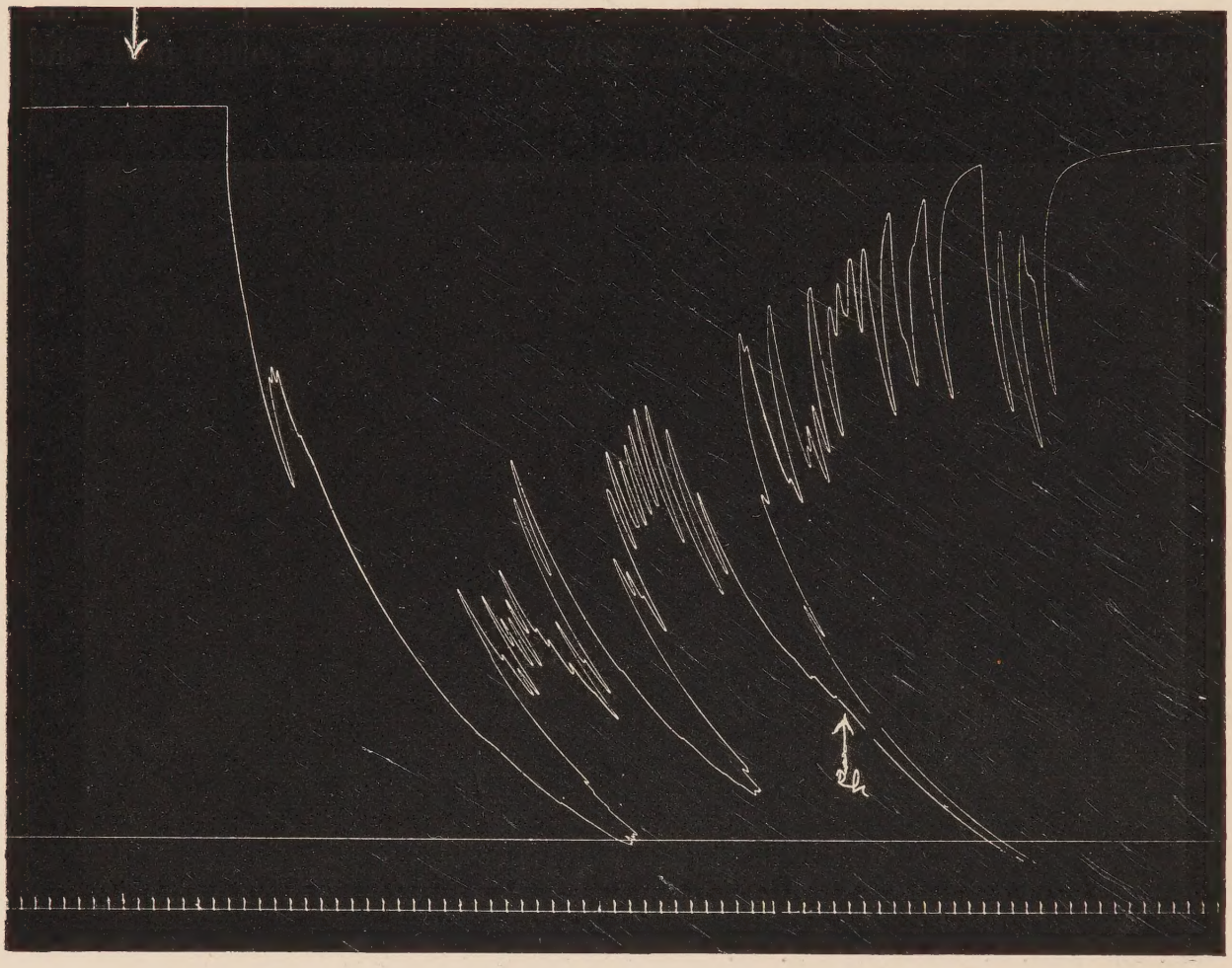


Fig. 13. Red. $\frac{2}{3}$. Isolated horn of pregnant cat's uterus. Effect of 2 mgms. *p.* hydroxyphenylethylamine. At ↓ the drug was added: change to pure Ringer's solution at ↑. Time = 10 seconds. Downstroke = Contraction.

but the effects passed off and the pregnancy terminated normally a week later. A pregnant goat was given 10 mgms. of *p.* hydroxyphenylethylamine by the ear-vein: a temporary slight dyspnœa and dilatation of the pupils was the only effect observed. Later 10 c.c. of $\frac{N}{10}$ isoamylamine hydrochloride was injected intraperitoneally into the same animal, again

without inducing labour, although the pregnancy was near its normal termination.

VI. The alimentary canal.

We recorded the movements of the small intestine in the dog, under morphia and A. C. E., by the balloon method, the recorder being a Marey's tambour. The same method was used in a cat with destroyed brain. In another decerebrate cat a loop of small intestine was closed at one end, filled with warm saline and connected to a manometer filled with the same fluid: the contractions were recorded by connecting the manometer to a Marey's tambour. In all cases the result was the same, when either *p.* hydroxyphenylethylamine or isoamylamine was injected intravenously, viz. a very brief inhibition of the tone and spontaneous rhythm of the muscular walls of the intestine.

An experiment was made with an isolated loop of rabbit's intestine: again inhibition of the spontaneous rhythm was produced by adding either base to the bath of Ringer's fluid, showing that the inhibitor effect is peripheral in origin and is a genuine, primary effect, and not a secondary result of the vasoconstriction.

The musculature of the frog's stomach and intestine differs from that of the mammal in receiving its motor nerve-supply from the true sympathetic (splanchnic) nerves. It was of interest, therefore, to observe its reaction to the bases under examination. A ring of frog's stomach was suspended between hooks so that it pulled on a lever against a weak spring. It was kept moist with 0·6 % saline and, when its slow rhythmic contractions had become regular, 0·1 % *p.* hydroxyphenylethylamine in 0·6 % saline was painted on it. The effect was powerful, tonic contraction of the ring, showing that, in this case again, the effect of the base corresponds to that of sympathetic nerves and of adrenaline.

Two points of difference from adrenaline should be noted here. First the inhibition of the mammalian intestines is of a much feebler nature than that caused by adrenaline, even when the effect on the blood-pressure is approximately the same in both cases. Secondly the motor effect on the frog's stomach is relatively more pronounced than that induced by adrenaline. Comment on these facts is reserved till later.

VII. The urinary bladder.

The experiments were made on the bladder of the decerebrate cat in which the hypogastric nerves had been cut to exclude sympathetic impulses from the spinal cord or the inferior mesenteric ganglia. The volume of the bladder contents was recorded by passing a catheter, connecting this to a wide reservoir half full of water, and again connecting the top of the reservoir to a Brodie's bellows. Both bases produced distinct inhibition of the tone and rhythm of the bladder. The effect was more conspicuous in the case of *p.* hydroxyphenylethylamine, and, even in this case, was weaker than that produced by such a dose of adrenaline as caused an approximately equal rise of blood-pressure (Fig. 14).

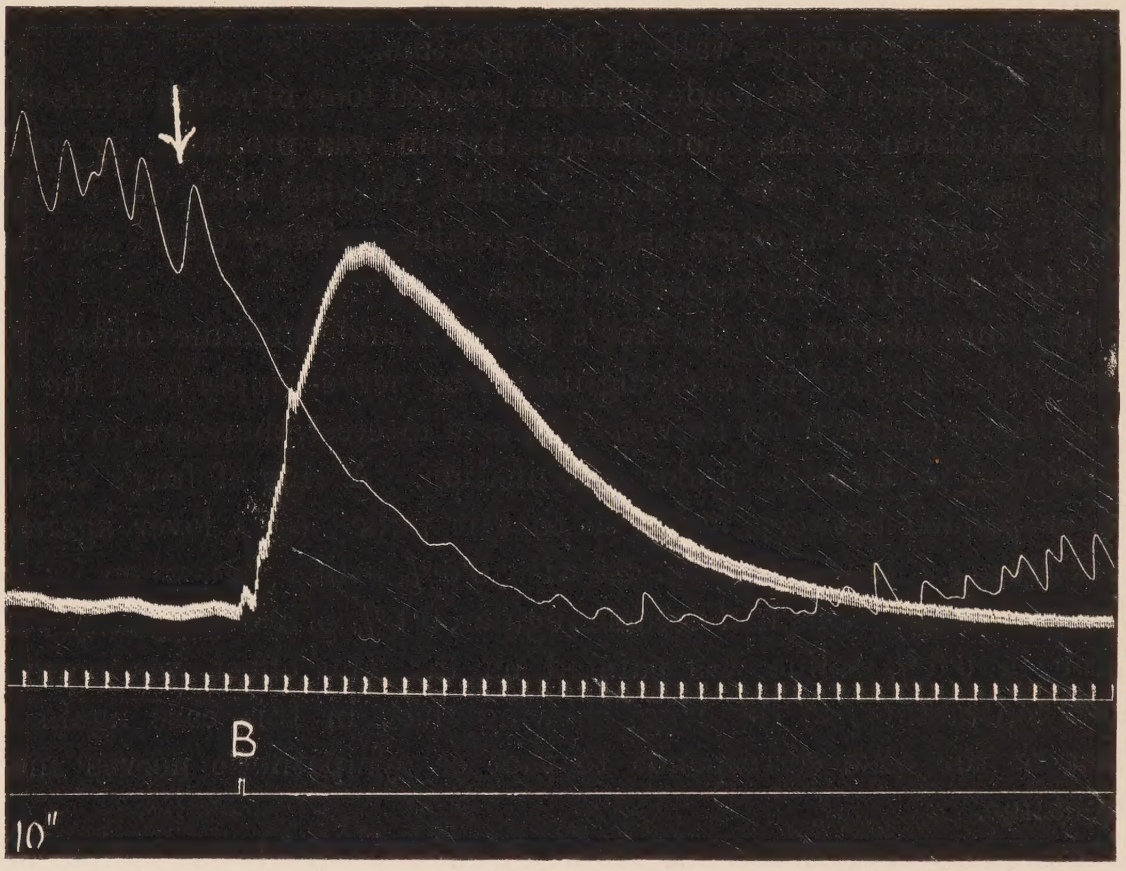


Fig. 14. Red. $\frac{2}{3}$. Pithed cat. Volume-record from urinary bladder and blood-pressure. At *B* 2 mgms. of *p.* hydroxyphenylethylamine were injected intravenously.

VIII. The involuntary musculature of the eye.

Intravenous injection of either *p.* hydroxyphenylethylamine or isoamylamine produces all the effects on the cat's eye and its surroundings caused by stimulation of the cervical sympathetic nerve or

injection of adrenaline, viz. dilatation of the pupil, retraction of the nictitating membrane, widening of the palpebral fissure, protrusion of the eyeball and secretion of tears. All these effects are still produced by either base and without preceptible modification, after extirpation of the superior cervical ganglion, and are, therefore, like the similar effects of adrenaline, peripheral in origin. Maximal dilatation of the pupils of enucleated frog's eyes was caused by 0·01 % *p.* hydroxyphenylethylamine and by $\frac{N}{100}$ isoamylamine.

IX. Gland cells.

It has been mentioned that both bases excite secretion of tears In a cat into which 100 mgms. of *p.* hydroxyphenylethylamine was injected hypodermically (vid. inf.) sweating of the pads of the feet was one of the effects noted. Secretion of the submaxillary gland of the cat was excited by both bases, but the effect of isoamylamine was relatively weak in this direction, only a few drops of saliva being obtained, in one instance, after an injection sufficient to cause a considerable rise of blood-pressure. *p.* hydroxyphenylethylamine has an effect very similar to that of adrenaline, though, as in the case of the effect on the blood-pressure, it is only about 1/20 as powerful. The following records of the effects of two successive injections show the approximately equal effects produced by 5 mgms. of *p.* hydroxyphenylethylamine and 0·2 mgm. of adrenaline respectively, the activity being, therefore, in this case about 1 : 25. It will be seen that the effect of the *p.* hydroxyphenylethylamine lasts considerably the longer, though the total amounts secreted are approximately equal. The figures show, in millimetres, the movement, in successive intervals of 10 secs., of the meniscus of the saliva along a narrow glass tube, placed horizontally, and connected to a cannula in Wharton's duct. The cat was under ether.

12.41 p.m.—0·2 mgm. adrenaline by jugular vein.

0, 0, 0, 0, 1, 3, 5, 4, 5, 4, 5, 3, 3, 1, 0, 0, 0, 0, 0,.....

↑ Injection

Total:—34 mm.

12.43½ p.m.—5 mgms. *p.* hydroxyphenylethylamine by jugular vein.

0, 0, 0, 3, 5, 4, 3, 3, 2, 2, 2, 1, 1·5, 1·5, 1, 1, 1, 0, 1, 0, 0·5, 0·5, 0,

↑ Injection

1, 0, 0·5, 0·5, 0, 0, 0·5, 0·5, 0, 0, 0, 0, 0, 0,.....

Total:—36 mm.

The administration of 1 mgm. of atropine diminishes but does not eliminate this action on the salivary glands.

Preliminary extirpation of the superior cervical ganglion is without effect on the result.

The pancreatic secretion is not perceptibly influenced by either of the bases. The flow of urine from the ureters is distinctly increased by both, and this is especially marked when the blood-pressure is initially low, as in the pithed cat: the effect is probably referable to the general rise of arterial pressure.

X. Effect of certain drugs.

After successive injections of nicotine, of such magnitude (26 mgms. in all) that further injections of that alkaloid no longer influenced the blood-pressure of a decerebrate cat, each of the amines produced a rise of blood-pressure somewhat less than that which it produced originally, but still very considerable. The effect of isoamylamine appeared to

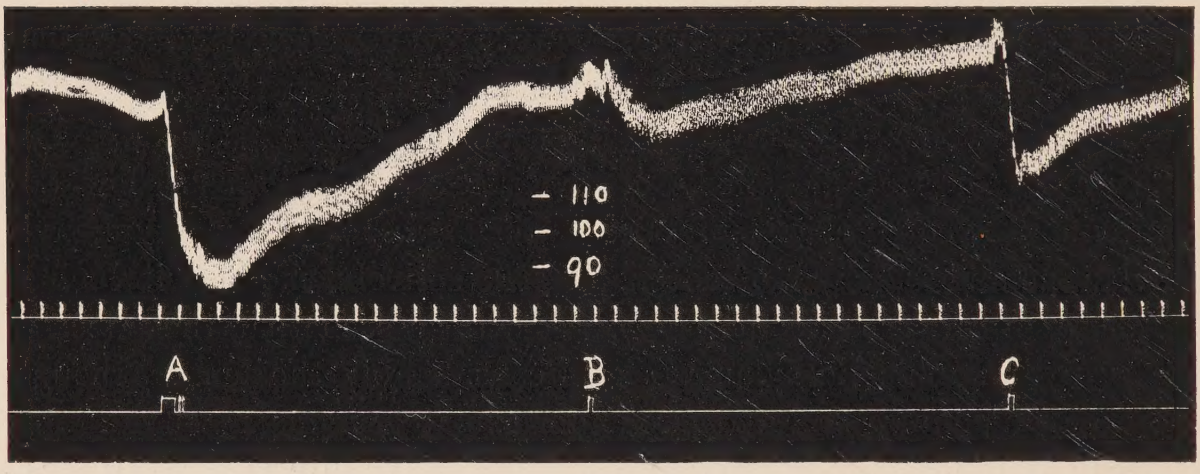


Fig. 15. Red. $\frac{2}{3}$. Blood-pressure of pithed cat. 5 mgms. of ergotoxine previously given intravenously. Time = 10 seconds.

At *A*—0·05 mgm. adrenaline
At *B*—2 mgms. *p.* hydroxyphenylethylamine
At *C*—2 c.c. $\frac{N}{10}$ isoamylamine hydrochloride
} intravenously.

suffer a greater reduction than that of *p.* hydroxyphenylethylamine, though it is difficult to be certain on this point on account of the progressively smaller effect of repeated doses, to which we have already drawn attention. The pressor effect of both bases, however, is clearly more affected by paralytic doses of nicotine than is that of

adrenaline: that is to say their effect is less strictly, though still mainly peripheral in origin.

Ergotoxine, which annuls the motor effects of sympathetic nerves and of adrenaline, so that the pressor effect of the latter is replaced by a fall of pressure due to vasodilatation, similarly affects the action of isoamylamine and of *p.* hydroxyphenylethylamine (Fig. 15). In the case of these bases, however, the fall of blood-pressure produced after ergotoxine is insignificant. This corresponds to what we have already described, being another instance, probably, of the comparatively weak excitation of inhibitory as compared with motor sympathetic effects.

XI. Channels of absorption.

It has been shown frequently that adrenaline causes so intense a local anæmia that its absorption from the alimentary canal or even from the subcutaneous tissues is too slow to allow its general effects to be observed when it is administered by the mouth or hypodermically.

The two bases under consideration produce far less local effect: *p.* hydroxyphenylethylamine, the more powerful of the two, applied to the conjunctiva in 1:1000 solution, causes a pallor which is so slight as to need careful comparison for its detection. Both, moreover, are far more stable than adrenaline, and it is not surprising to find that they produce their general effects even when given hypodermically or by the alimentary canal. We found that 10 c.c. $\frac{N}{10}$ isoamylamine hydrochloride, injected into the rectum, produced a slow, steady rise of blood-pressure in a decerebrate cat in which the pressure had previously been slowly declining. 100 mgms. of *p.* hydroxyphenylethylamine, injected hypodermically into a cat, caused the appearance, after 2 minutes, of all the symptoms of stimulation of sympathetic nerves to an intense degree. The pupils dilated to their maximum and ceased to respond to light; there was a flow of tears and profuse salivation; the paws became moist with sweat, which could be seen exuding in beads from the pores of the hairless pads; the heart-beat became violent and interrupted, apparently by reflex vagus inhibition; respiration was rapid, the mouth being open; the sphincter ani internus was contracted to a degree which made the insertion of a clinical thermometer a matter of some difficulty. The cat showed some, but not severe prostration: the temperature rose to 104° F. The pupils began to react again to

light 30 minutes after the injection and the effects then gradually subsided. The urine, collected for the following 24 hours, contained neither albumin nor sugar and the cat remained completely normal while under observation.

An experiment upon one of ourselves, who took 10 mgms. of *p.* hydroxyphenylethylamine by the mouth on an empty stomach, indicated the rapid absorption of this base from the alimentary canal. The observation is in accordance with the clinical evidence as to the efficacy of ergot extracts so administered. The following are the readings of the arterial blood-pressure obtained at 5 minutes intervals, with Martin's Riva-Rocci apparatus.

Moving about	Resting		10 mgms. *p.* hydroxyphenyl-ethylamine in water ↓						
120,	115,	116,		124,	136,	149,	148,	135,	136,
				Micturition ↓		30 minutes interval for a meal			
135,	135,	134,	134,		122,	.....			130

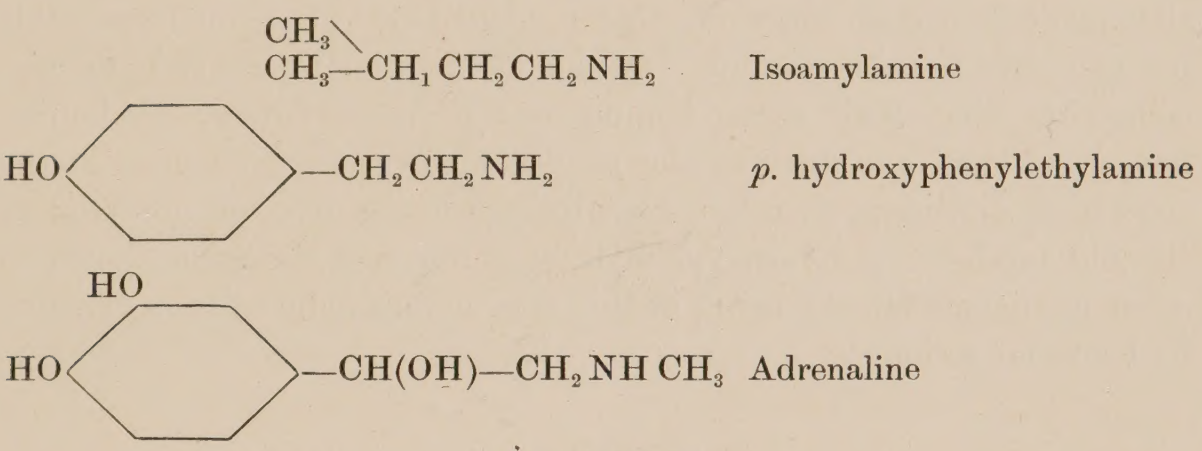
It will be seen that the pressure was still distinctly raised 85 minutes after the dose, when the readings were discontinued. During the highest portion of the rise some feeling of fulness in the head was experienced and the face was flushed: the heart-beat was powerful and slightly intermittent and the breathing became rather deeper. No salivation, perspiration or dilatation of the pupil was observed, and no nausea or malaise was produced. The urine was examined subsequently without the detection of sugar or albumin. No obvious after-effects were perceptible. The sudden necessity for micturition during the experiment suggested an increased secretion of urine, but careful controls would be needed before this could be accepted as proved.

XII. Discussion of results.

It is clear from the foregoing account that the action of both these bases has a marked similarity to that of adrenaline. Their chemical relation to that body, and to one another, as exhibited by their structural formulae (p. 43), is a clear though not a close one.

The whole question of the relationship of chemical structure to this particular action is at present under examination by one of us (H. H. D.) in conjunction with G. Barger. It is here more important to note the

differences between the actions of these bases. It has already been pointed out that the reduction of the effect of both isoamylamine and *p.* hydroxyphenylethylamine by nicotine indicates that their action is not strictly limited to the periphery. Destruction of the spinal cord similarly diminishes their effect on the blood-pressure, and, like the effect of nicotine, reduces the effect of isoamylamine more than that of *p.* hydroxyphenylethylamine. On the other hand the peripheral effect of *p.* hydroxyphenylethylamine appears to have the same limits as that of adrenaline, being restricted to such muscle-fibres and gland-cells as receive a sympathetic nerve supply, and affecting their action in the



same sense, whether of augmentation or inhibition, as the sympathetic nerves. The peripheral effect of isoamylamine is in the main similar: in the case of structures supplied by sympathetic nerves it reproduces the action of the latter. Its action, however, is not strictly limited to such structures, since it causes constriction of the pulmonary and, probably, of the coronary arterioles. The effects of both bases, in so far as they reproduce motor actions corresponding with sympathetic excitation, are affected by ergotoxine in the same way as those of adrenaline. Both reproduce the inhibitor actions of the sympathetic system with less intensity than its motor effects.

While both bases when injected in sufficient doses into the circulation, thus produce specific effects on plain muscle and gland-cells closely resembling those of adrenaline, they differ from it in having much less general toxicity. Also their weaker local effect enables them to be absorbed much more readily from the subcutaneous tissues and through mucous membranes. The effects of sympathetic stimulation can thus be produced by these amines in a much less sudden and more persistent form. It is probable, indeed, that the effects of *p.* hydroxy-

phenylethylamine are already known and used in therapeutics, being produced by active specimens of the official ergot extracts.

The fact that the amines can be absorbed from the alimentary canal and produce their effects is also of special interest in connexion with the observation of Barger and Walpole that *p.* hydroxyphenylethylamine can be produced by allowing fæcal bacteria to grow in a medium containing tyrosine. Many observations have been published recently concerning the presence in the blood-serum and urine, in various pathological conditions, of substances which cause dilatation of the pupil of the enucleated eye of the frog. The fact that both these amines have this action casts some doubt at least on the validity of the assumption, made by certain observers, that the substance in serum, responsible for this effect, is adrenaline. It should also be mentioned, in this connexion, that both isoamylamine and *p.* hydroxyphenylethylamine have been shown to arise as the result of putrefactive changes in the cod's liver, and were, therefore, constituents of cod-liver oil prepared by the old method. *p.* hydroxyphenylethylamine has also been shown to occur in ripened cheese, being in this case again produced from tyrosine by bacterial action.

Summary.

1. Both isoamylamine and *p.* hydroxyphenylethylamine have an action which is very similar to that of adrenaline, reproducing both the motor and inhibitory effects of nerves of the true sympathetic system. Both, however, produce the motor more powerfully than the inhibitory effects.

2. Their action differs from that of adrenaline in being weaker and slower in onset, isoamylamine being much the weaker of the two, and in being less strictly though still mainly peripheral.

3. Both are absorbed from the subcutaneous tissues and the alimentary canal and produce their effects when so administered.